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ORIGINAL ARTICLE

Association of Angiotensin-Converting Enzyme Inhibitor Therapy Initiation With a Reduction in Hemoglobin Levels in Patients Without Renal Failure

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Abstract

Objective: To investigate whether treatment initiated with an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin II receptor blocker (ARB) for patients with ischemic heart disease, hypertension, or diabetes causes a reduction in hemoglobin (Hb) levels.

Patients and Methods: This was a retrospective cohort analysis using the computerized database of a large health maintenance organization. Included were all adults with a first purchase of an ACE-I, an ARB, or a calcium channel blocker (CCB) between January 1, 2004, and December 31, 2009, defined as the index date. Measures of Hb levels before and 1 year after the index date were reviewed, and the change was calculated. All the analyses were stratified by pharmaceutical class. The main exposure variables were the proportion of days covered (PDC) by these drugs and the mean enalapril dosage (for enalapril users only).

Results: Levels of Hb before and after treatment were available for 14,754 patients taking ACE-Is, 751 taking ARBs, and 3087 taking CCBs. A high PDC was significantly associated with greater yearly reductions in Hb levels compared with a low PDC for CCB use, but was more pronounced for ACE-I and ARB use. A high PDC was also associated with a higher odds of developing anemia in ACE-I users (odds ratio [OR], 1.59; $P<.001$) and ARB users (OR, 2.21; $P=.05$). In nonanemic enalapril users, every 10-mg increment in daily dose was associated with an OR of 1.45 for the development of anemia ($P<.001$). The association remained after excluding nonadherent patients.

Conclusion: Levels of Hb are reduced during the first year of use of ACE-Is and to a lesser extent with use of ARBs. This association is dose dependent and is not explained by patient adherence.

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Angiotensin-converting enzyme (ACE) plays a role in hematopoiesis stimulation and not only in the regulation of vascular homeostasis.[1] Several studies have found that renin angiotensin system activation may enhance erythropoiesis and may be associated with secondary erythrocytosis.[2,3] The ACE inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) have been reported to reduce hemoglobin (Hb) levels in several patient groups at risk for secondary erythrocytosis, including patients with heart failure,[4] hemodialysis,[5] or chronic obstructive pulmonary disease,[6,7] and after cardiac surgery[8] or kidney transplant.[9,10] Although the physiologic mechanism for the observed inhibitory effect remains unclear, these pharmaceutical classes were found to suppress erythropoiesis in the previously mentioned populations in a dose-dependent manner. Moreover, treatment with ACE-Is or ARBs has been proved effective for secondary polycythemia, for example, after renal transplantation[9] and reactive high-altitude erythrocytosis.[11] To date, large-scale population-based studies regarding the hematologic effect of these common medications in patients with heart disease, hypertension, and diabetes with preserved renal function have not been performed, to our knowledge. The aim of this study was to evaluate the association between initiation of ACE-I or ARB therapy and Hb concentration in patients receiving these drugs for reasons not associated with secondary erythrocytosis.

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PATIENTS AND METHODS

Study Population

We conducted a retrospective cohort study using the database of Maccabi Healthcare Services (MHS), Israel's second largest health care maintenance organization, described in detail elsewhere.[12-14] Briefly, the MHS database (fully in use in all levels of the

organization) has been operational since 1996 and currently includes the medical history and laboratory data of approximately 2 million individual members of MHS, which under the Israeli National Health Insurance Act may not bar any citizen who wants to join it.

All the data were obtained from the MHS computerized database used to elicit information on all community consultations, diagnoses, prescriptions, dispensed prescriptions, hospital discharge data, laboratory test results, and other treatments. The diagnosis dates are entered automatically as the encounter dates or by the physician for specific event dates. The analysis was performed retrospectively using a large unnamed database and was approved by the Institutional Review Board of Assuta Medical Center, Tel Aviv, with a waiver of informed consent.

Cohort Definition

The present retrospective analysis included all MHS members older than 25 years with a record of at least one purchase from one of the following pharmaceutical classes: ACE-Is, ARBs, or calcium channel blockers (CCBs) from January 2004 through December 2009. The date of the first purchase was defined as the index date. We excluded all patients with purchases of ACE-Is, ARBs, or CCBs during the previous years (2001-2003) and patients with purchases of medications from more than one of these pharmaceutical classes (ACE-Is, ARBs, and CCBs) during the first 15 months after the index date.

The initial cohort using the MHS central database included adults older than 25 years starting treatment with an ACE-I, ARB, or CCB between January 1, 2004, and December 31, 2009, and receiving only that pharmaceutical class during the first 15 months after the index date. To assess the true reduction in Hb levels in patients in the general population receiving these medications, we excluded all patients with renal failure (a diagnosis or an estimated glomerular filtration rate <60 ml/min using the simplified Modification of Diet in Renal Disease formula[15]), cancer, pregnancy, major bleeding, and surgical ward hospitalization in the year before the index date and during the following year. Individuals with more than 10 measurements of Hb levels during 1-year follow-up were also excluded because these measurements may have obscured an alternative medical problem.

After applying the exclusion criteria noted previously herein, the cohort included 17,960 patients taking ACE-Is, 916 receiving ARBs, and 3884 taking CCBs (N=22,760). Annual change in Hb level was available for 81.7% of these patients (n=18,592) having an Hb level measurement before treatment initiation and at least one Hb level measurement during the 15 months after the index date. A total of 14,754, 751, and 3087 patients receiving ACE-Is, ARBs, and CCBs, respectively, were eligible for the analyses.

Hb Level Measurements

For each patient, the following Hb measures were reviewed: the last Hb level before the initiation of ACE-I, ARB, or CCB therapy during the 6 months before to1 month after the index date and the last Hb level recorded 9 to 15 months after the index date. To evaluate the change in Hb levels during 1 year, we calculated the mean yearly difference in Hb levels (delta of Hb change normalized for a 1-year period using the time difference between the measures). Anemia status for each Hb measurement was defined as Hb levels less than12 g/dL in women and less than 13 g/dL in men (to convert to g/L, multiply by 10.0), in accordance with the World Health Organization (WHO) criteria.[16] Measurements of Hb levels were performed using automated hematology analyzers (Sysmex XE-5000 or Sysmex XE-2100; Sysmex Corp) at various central laboratories across Israel.

Proportion of Days Covered

In accordance with previous studies,[14,17,18] we calculated the mean proportion of days covered (PDC) by dividing the quantity of study medication dispensed by the interval from the index date to the end of follow-up, death, leaving MHS, or December 31, 2009, whichever occurred first. We excluded individuals with a PDC greater than 120% because these extra purchases might indicate errors rather than real extra exposure.

Statistical Analyses

All the analyses were stratified by pharmaceutical class and were adjusted for sex and age category by decades. Linear regression analyses were used with mean Hb level difference as a dependent variable, and logistic regression analyses were used with development of anemia as a dependent variable. The main exposure variables were PDC (duration of dispensed prescriptions divided by follow-up time) and mean enalapril dosage (for enalapril users only). The PDC was categorized into 3 levels: low ($<$33%), medium (33%-66%), and high ($>$66%-100%).

Factors with possible influence on Hb level, in addition to other comorbidities, were extracted from the database to enable adjustments in multivariate models: age (categorized into decades), sex, and exposure to statins, warfarin, clopidogrel, enoxaparin, heparin, fibrates, and nitrates (defined as $\geq$1 purchase during the year after the index date). The final models were adjusted only for age and sex because further adjustment for additional character-

TABLE 1. Basic Population Description, Comorbidities, and Relevant Medications[a,b]

Variable	Total cohort (N=18,592)	ACE-I users (n=14,754)	ARB users (n=751)	CCB users (n=3087)
Age (y), mean ± SD (range)	55±11 (25-96)	55±11 (25-96)	57±11 (29-93)	57±12 (25-96)
Male	9776 (53)	8022 (54)	393 (52)	1361 (44)
Hypertension	14,011 (75)	11,189 (76)	525 (70)	2297 (74)
Diabetes	4753 (26)	4338 (29)	182 (24)	223 (7)
Cardiac registry	2942 (16)	2363 (16)	134 (18)	445 (15)
Combined hypertension, diabetes, and cardiac registry	16,644 (89.5)	13,496 (91.5)	633 (84.3)	2515 (81.5)
Clopidogrel	1204 (7)	1084 (7.3)	40 (5.3)	80 (2.6)
Warfarin	416 (2.2)	296 (2)	21 (2.8)	99 (3.2)
Heparin	1 (0)	1 (0)	0	0
Enoxaparin	195 (1)	141 (1)	9 (1.2)	45 (1.5)
Statins	10,269 (55)	8492 (57.6)	434 (57.8)	1343 (43.5)
Fibrates	930 (5)	788 (5.3)	39 (5.2)	103 (3.3)
Nitrates	551 (3)	439 (3)	19 (2.1)	93 (3)

[a] ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.
[b] Data are presented as No. (percentage) of patients unless indicated otherwise.

istics (comorbidites and other medication exposure), as well as stratification by sex, did not reveal major changes (data not shown). All the analyses were performed using a statistical software package (SPSS, version 19; SSPS Inc). $P<.05$ (2-tailed) was considered significant.

RESULTS

The final cohort included 14,754, 751, and 3087 patients receiving ACE-Is, ARBs, and CCBs, respectively, eligible for the analyses. The mean ± SD patient age was 55±11 years (age range, 25-96 years). Men composed 53% of the study population. Table 1 presents the basic characteristics, comorbidities, and relevant medications used by the study patients. During 1-year follow-up, 233 patients (1.6%), 14 (1.9%), and 32 (1.0%) treated with ACE-Is, ARBs, and CCBs, respectively, developed anemia according to the WHO definition. Measurements of Hb levels before and after treatment initiation are given in Table 2. A significant reduction in Hb concentrations was noted 1 year after treatment initiation with each of the 3 medications (Figure 1), although the average change in Hb level in patients receiving CCBs was smaller (Table 2).

Mean annual change in Hb level was calculated separately for the 3 PDC levels, reflecting adherence to medical treatment with the tested medications. The PDC with ACE-Is was associated with a mean annual reduction in Hb levels of 0.07 and 0.15 g/dL comparing medium and high adherence with patients in the low PDC group, respectively. A similar

TABLE 2. Measurements of Hb Levels Before Treatment Initiation and After 1 Year of Treatment[a,b]

		Before treatment initiation				After treatment initiation			
Pharmaceutical class	Patients (No.)	Mean Hb (g/dL)	Hb range (g/dL)	IQR	Patients with anemia (No. [%])[c]	Mean Hb (g/dL)	Hb range (g/dL)	IQR	Patients with anemia (No. [%])[c]
ACE-I	14,754	14.07	7.3-21.9	13.1-15.1	1207 (8.2)	13.94	7.4-19.7	13.0-14.9	1440 (9.8)
ARB	751	13.99	6.6-17.4	13.1-14.9	67 (8.9)	13.87	8.5-18.2	12.9-14.8	81 (10.8)
CCB	3087	13.89	8.5-20.2	13.0-14.8	284 (9.2)	13.83	8.0-21.0	12.9-14.8	316 (10.2)

[a] ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; Hb = hemoglobin; IQR = 25%-75% interquartile range.
[b] SI conversion factor: To convert Hb values to g/L, multiply by 10.0.
[c] Anemia according to the World Health Organization definition: Hb levels <12 g/dL in women and <13 g/dL in men.

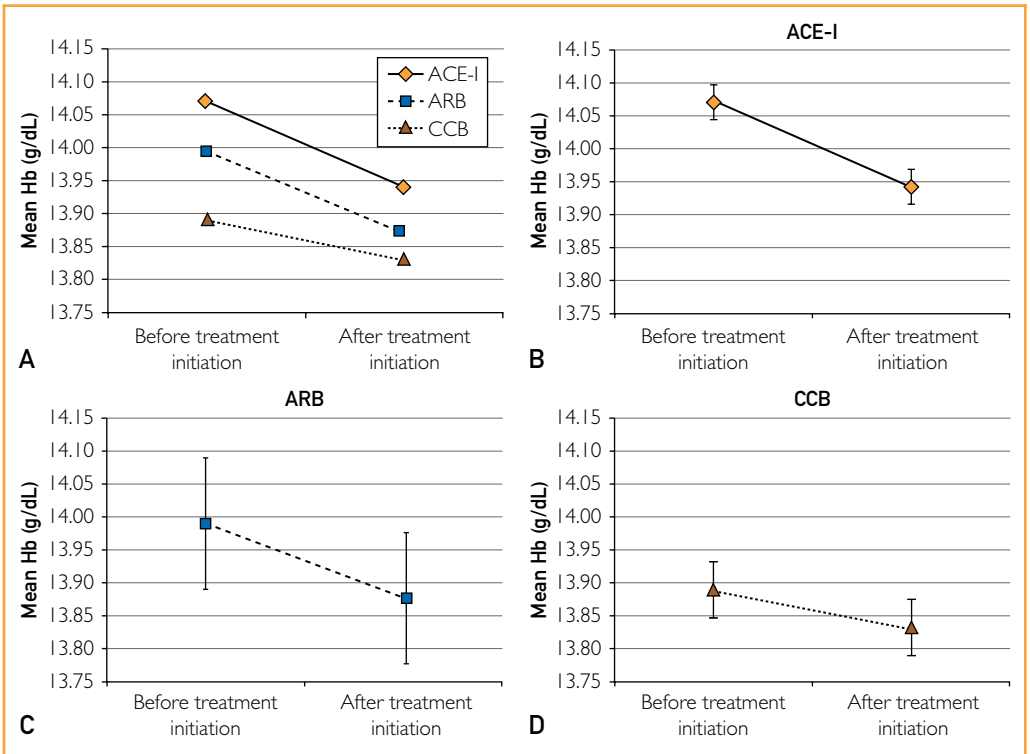

FIGURE 1. Mean change in hemoglobin (Hb) levels before and after treatment initiation (A) for all 3 pharmaceutical classes and individually for (B) 14,754 individuals receiving angiotensin-converting enzyme inhibitors (ACE-Is), (C) 751 receiving angiotensin II receptor blockers (ARBs), and (D) 3087 receiving calcium channel blockers (CCBs). Paired *t* test; statistically significant ($P<.001$) change for each pharmaceutical class. Error bars represent standard error of mean.

association was also observed in patients treated with ARBs in the high-adherence group. A high PDC for CCB treatment was associated with a reduction in Hb levels of 0.08 g/dL compared with patients with a low PDC (Table 3).

Using a logistic regression model, we examined the association of medication adherence with the development of anemia in accordance with WHO criteria in patients who were not anemic at baseline, revealing significant odds of progression to anemia during 1 year of follow-up in patients with a high PDC receiving ACE-Is or ARBs (odds ratios [ORs],1.59 and 2.21, respectively) but not in patients taking CCBs (Table 3). A statistically significant OR for anemia development in the medium PDC group was found only with ACE-I treatment.

To better assess the biological exposure to ACE-Is and reduce the influence of patient adherence, we performed additional analyses for a subset of patients who purchased only enalapril (in its various brand names and dosages) during the study period (8466 patients, 57.4% of the ACE-I group). For each of these patients, we summed the total amount of enalapril purchased and divided by the time of follow-up to calculate the mean daily consumption dose of enalapril.

The annual change in Hb levels was found to be associated with enalapril quintile in a dose-response pattern (Figure 2). Multivariate models, adjusted for age and sex, revealed that every daily 10 mg of enalapril is associated with an annual reduction in Hb levels of 0.16 g/dL ($P<.001$) and increased odds of progression to anemia (OR, 1.45; $P<.001$). To totally eliminate the adherence component from the exposure estimate, we further restricted the population to patients with very high enalapril adherence levels (PDC >80%). In this sample, every daily 10 mg of enalapril was associated with an annual reduction in Hb levels of 0.08 g/dL ($P=.001$), but progression to anemia was not significantly associated with enalapril dosage (OR, 1.17; $P=.16$) (Table 4).

DISCUSSION

We found that treatment with ACE-Is and ARBs in the general population receiving these common medications for the treatment of ischemic heart dis-

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TABLE 3. Annual Difference in Hb Levels and Development of Anemia Compared With the Low PDC (<33%) Group[a,b]

Pharmaceutical class	Patients (No.)	Medium PDC (33%-66%) group		High PDC (>66%-100%) group	
		B or OR (95% CI)[c]	*P* value	B or OR (95% CI)[c]	*P* value
Model 1: Annual Hb difference (g/dL)					
ACE-I	14,754	–0.07 (–0.11 to –0.03)	<.001	–0.15 (–0.18 to –0.12)	<.001
ARB	751	–0.02 (–0.16 to 0.21)	.80	–0.16 (–0.29 to –0.02)	.02
CCB	3087	–0.02 (–0.11 to 0.07)	.65	–0.08 (–0.15 to –0.02)	.008
Model 2: Development of anemia (according to WHO criteria)[d]					
ACE-I	13,547	1.39 (1.12 to 1.73)	.003	1.59 (1.34 to 1.88)	<.001
ARB	684	1.43 (0.46 to 4.43)	.54	2.21 (1.01 to 4.81)	.05
CCB	2803	1.04 (0.64 to 1.68)	.88	0.73 (0.51 to 1.05)	.09

[a] ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; B = beta coefficient; CCB = calcium channel blocker; Hb = hemoglobin; OR = odds ratio; PDC = proportion of days covered; WHO = World Health Organization.
[b] Annual difference in Hb levels is defined as the absolute change in Hb levels between measurements divided by the number of days between measurements/365.
[c] B for both models (adjusted for sex and age) and OR for model 2.
[d] Only for nonanemic patients at baseline.

ease (IHD), diabetes, and hypertension is associated with an increased risk of anemia and a reduction in Hb levels during the first year after the commencement of therapy with these pharmaceutical agents. These results indicate that the apparent reduction in Hb levels seen in patients prone to secondary erythrocytosis due to concomitant medical conditions exists also in patients without such conditions and with normal renal function.

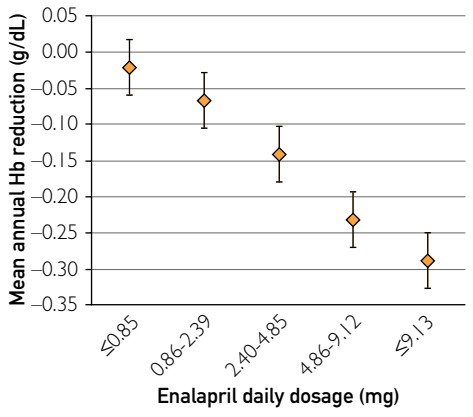

FIGURE 2. Annual changes in hemoglobin (Hb) levels according to daily enalapril dosage in a patient subset purchasing only enalapril (8466 patients, 57.4% of the angiotensin-converting enzyme inhibitor group). The changes were found to be associated with daily enalapril dosage quintiles in a dose-response pattern. Error bars represent SD of the mean.

More specifically, using a large population database, we found that in the first year after the initiation of ACE-I or ARB therapy, patients with high adherence to medical treatment had a significant reduction in Hb levels compared with noncompliant individuals. This association was also observed with medium-level adherence, but only in patients taking ACE-Is.

We next evaluated whether these reductions in Hb levels consequently have clinical meaning and found increased odds of progression to anemia (WHO criteria) in patients starting ACE-I or ARB treatment and adhering to therapy. A similar association was not found when applying the same method to a cohort of CCB users.

A different look at exposure to ACE-Is taking into consideration medication dosage revealed a dose-dependent association between enalapril daily dosage and reduction in Hb levels. The association existed even after analyzing only highly adherent patients, although its magnitude was reduced by a factor of 2. This finding suggests that healthy user bias, if it existed in the present study, was limited to a maximum of half of the association between adherence and reduction in Hb levels. The fact that adherence to CCB therapy also showed associations that were reduced by a factor of 2 also supports this interpretation.

To our knowledge, the impact of ACE-I and ARB use on inhibition of the positive hematologic effects of renin-angiotensin system activation has

TABLE 4. Enalapril Exposure and Change in Hb Levels (for Enalapril Users Only)[a]

Enalapril (per 10 mg/d)	Patients (No.)	B or OR (95% CI)[b]	*P* value
Linear regression model: annual change in Hb levels according to enalapril daily dosage			
Any PDC level	8466	–0.16 (–0.19 to –0.13)	<.001
PDC >80%	2459	–0.08 (–0.13 to –0.04)	.001
Logistic regression model: development of anemia (WHO criteria) according to enalapril daily dosage[c]			
Any PDC level	7810	1.45 (1.26 to 1.67)	<.001
PDC >80%	2541	1.17 (0.94 to 1.45)	.16

[a] B = beta coefficient; Hb = hemoglobin; OR = odds ratio; PDC = proportion of days covered; WHO = World Health Organization.
[b] B for the linear regression model (both models adjusted for sex and age) and OR for the logistic regression model.
[c] Only for nonanemic patients at baseline.

been studied thoroughly only in patient populations at risk for secondary erythrocytosis[5-11] but not in most patients taking these pharmaceuticals for indications such as diabetes, hypertension, IHD, and left ventricular dysfunction.

Study Limitations

This study has several limitations that should be considered. Community physicians' rationale for obtaining measurements of Hb levels before treatment initiation and during follow-up is not known because it was acquired at the discretion of the treating physician. In addition, the nature of this study, being observational and retrospective, forced us to exclude patients (>4000) in whom measures of Hb levels were not available during the year after treatment initiation.

To assess the true effect of treatment with these pharmaceutical classes on anemia status, we excluded patients in whom an excessive number of blood tests (≥10) were performed during the 1-year follow-up because these measurements may have obscured an alternative medical problem. Even so, these data are derived from a large database, and, therefore, the Hb range extremes are influenced by single patients possibly experiencing unrelated medical conditions. An additional limitation is that the associations observed herein do not allow us to draw conclusions of a causal relationship, and future clinical trials will be able to determine this issue.

Perspectives

Initiation of treatment with ACE-Is and ARBs produces a reduction in Hb levels also in patients who are not at risk for secondary erythrocytosis. Because these medications are broadly used in conditions in which anemia and Hb reduction are associated with worse prognosis (eg, IHD), further research is needed to reveal the underlying mechanism and the clinical consequence of these findings.

CONCLUSION

The present findings support the claim that Hb levels are reduced during the first year after initiation of treatment with ACE-Is or ARBs. This association is dose dependent and cannot be totally explained by artifacts related to patient adherence. These findings reveal that reduced Hb levels in the general population receiving ACE-I or ARB therapy not only might be due to an unknown underlying mechanism affecting patients with secondary erythrocytosis, who are particularly sensitive to factors inhibiting erythropoiesis, but is also probably a class effect of ACE-I treatment and of ARB use to a lesser extent.

Abbreviations and Acronyms: **ACE-I** = angiotensin-converting enzyme inhibitor; **ARB** = angiotensin II receptor blocker; **CCB** = calcium channel blocker; **Hb** = hemoglobin; **IHD** = ischemic heart disease; **MHS** = Maccabi Healthcare Services; **OR** = odds ratio; **PDC** = proportion of days covered; **WHO** = World Health Organization

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